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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,407	08/01/2003	Douglas W. Losordo	58098 (71417)	6007

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EXAMINER	
HISSONG, BRUCE D	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
10/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,407	LOSORDO ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/23/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-83* is/are pending in the application.

4a) Of the above claim(s) *4-7,10,14-16,20,22,23,28,29,35,43-65 and 69-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 8-9, 11-13, 17-19, 21, 24-27, 30-34, 36-42, 66-68, and 75-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/23/2008 has been entered.

2. In the response received on 6/23/2008, Applicants added new claims 77-83. Therefore, claims 1-83 are currently pending, with claims 4-7, 10, 14-16, 20, 22-23, 28-29, 35, 43-65, and 69-74 withdrawn as non-elected subject matter. Claims 1-3, 8-9, 11-13, 17-19, 21, 24-27, 30-34, 36-42, 66-68, and 75-83 are the subject of this office action.

Claim Objections

1. The Examiner suggest amending claim 30 to remove the extra space between “vessels” and the following comma (i.e. amend "vessels , wherein the decrease" to instead read "vessels, wherein the decrease".

2. The Examiner suggests amending claim 80 to recite "The method of claim 30, wherein", rather than "The method of claim 30 ,. wherein". In other words, there is an extra space before the comma.

3. The Examiner suggests amending claim 82 to recite “wherein the endothelial cells are contacted”.

Claim Rejections - 35 USC § 112, first paragraph – written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection withdrawn

1. Rejection of claims 1-3, 8, 11-13, 17-19, 21, 24-27, 30-33, 36-42, and 66-68 under 35 USC § 112, first paragraph, regarding lack of written description for the genus of ezrin modulating agents, as set forth on pages 2-4 of the prior office action mailed on 1/23/2008 and pages 2-4 of the office action mailed on 5/1/2007, is *withdrawn*.

In the response received on 6/23/2008, the Applicants argue that the Examiner's reliance on *University of Rochester v G.D. Searle & Co.* ("*Rochester*" – citation omitted) is misplaced because the instant application differs from *Rochester* in that *Rochester* disclosed a new gene and protein for which no agonists or antagonists were known. In contrast, the Applicants assert that the instant application recites a genus of compound, namely ezrin modulators, that were known at the time of invention. Specifically, the Applicants argue that in addition to Y27632, a dominant negative ezrin polypeptide was known, as were TNF antagonists and anti-TNF antibodies, as well as Rho kinase inhibitors. The specification teaches that Y27632 is simply a preferred inhibitor.

The Applicants also argue that the claims are drawn to a method, rather than a composition, and the specification teaches the role of ezrin in mediating proliferation of endothelial cells in response to TNF-α, which is frequently produced as a result of blood vessel damage and ischemia. As the proteins in this pathway were all known at the time of filing, inhibitors and activators of the compounds were known and their methods of use were understood by those of skill in the art. Thus, having disclosed the pathway in the instant application, one of skill in the art would know how to practice the invention with any of a number of agents that would modulate signaling through the pathway. In the instant case, what is claimed are methods of modulating endothelial cell proliferation by modulating ezrin activity, methods of inducing new blood vessel formation by decreasing ezrin activity, and methods of reducing the severity of blood vessel damage by decreasing ezrin activity. The claimed methods only require modulating ezrin activity in a mammal by administering an ezrin modulating agent, and the instant specification has exemplified working examples of modulating ezrin using Y27632 and a dominant-negative ezrin.

Therefore, because the claims are drawn to methods comprising modulating ezrin with agents that have been described in the art, and have exemplified working examples using two ezrin modulators, one of ordinary skill in the art would recognize that the Applicants were in possession of the claimed genus of ezrin modulators at the time the application was filed.

These arguments have been fully considered and are persuasive in that the claims are drawn to methods of decreasing ezrin activity, and Applicants arguments that the specification and the art disclose numerous agents capable of decreasing ezrin activity.

Claim Rejections - 35 USC § 112, first paragraph - enablement

Claims 1-3, 8-9, 11-13, 17-19, 21, 24-27, 30-34, 36-42, 66-68, and 75-76 *remain rejected* , and new claims 77-83 are also rejected under 35 USC § 112, first paragraph, regarding lack of enablement for the claimed methods of modulating endothelial cell proliferation comprising administration of an ezrin modulating agent, as set forth on pages 4-8 of the office action mailed on 1/23/2008.

In the response received on 6/23/2008, the Applicants argue that Shibata teaches prevention of neointimal lesion formation by administering the ROCK2 inhibitor Y27632, and that the inhibitor is proposed to work by promoting smooth muscle cell apoptosis. The Applicants assert that neointimal lesion formation is distinct from angiogenesis and is never desirable.

The Applicants also note that the claims recite methods of contacting endothelial cells *ex vivo* with enzrin modulating agents, and to methods of local administration of ezrin modulating agents. Methods of local delivery of ezrin modulating agents can be performed by methods known in the art, and ezrin can also be delivered for a short time, such as when TNF-α levels are elevated. This is in contrast to Shibata, which states that some of the effects seen in the study may be due to long-term administration of the compound (Y27632). The Applicants note that methods of dosing and monitoring a subject for a response to a therapeutic agent are well within the skill of the art, and therefore the problems noted in Shibata can be avoided.

Furthermore, in relation to the teachings of Van Nieuw Amerongen, the Applicants argue that "wounding" of a culture *in vitro* does not result in an inflammatory response, such as the release of TNF-α, and Van Nieuw Amerongen teaches activity of Rho kinase inhibition in relation to VEGF-stimulated migration, rather than TNF-α-induced proliferation, and angiogenesis requires both migration and proliferation.

Finally, the Applicants argue that the specification satisfies the requirement of *Cross v. Izuka* by providing a reasonable correlation between the *in vitro* data and the *in vivo* ischemia model presented in Example 14 of the specification. The Applicants argue that a mouse is a "complex biological system", and in this mouse model, an ezrin modulating agent was administered to a mouse with damaged vasculature, resulting in blood flow recovery relative to a control animal. In this complex biological

system, angiogenesis occurred despite suggestions of other references that angiogenesis might be inhibited by inhibition of Rho kinase. Therefore, because the ezrin-modulating agents have been demonstrated *in vitro* to inhibit Rho kinase and ezrin activity, and this is correlated with *in vitro* endothelial cell migration, one of ordinary skill in the art would expect that ezrin-modulating agents would act in a similar manner *in vivo*.

These arguments have been fully considered and are not persuasive. The issue at hand is whether one of ordinary skill in the art would conclude that administration of an ezrin inhibitor such as Y27632 would modulate proliferation of endothelial cells, promote formation of new blood vessels, and/or reduce the severity of blood vessel damage. The specification shows that inhibiting Rho kinase-dependent phosphorylation of ezrin relieves TNF/ezrin-mediated inhibition of endothelial cell proliferation *in vitro*, and also shows that transplantation of dominant-negative ezrin-transfected HUVECs improves blood flow recovery in a nude mouse model of hind-limb ischemia. Based on these observations, the Applicants assert that administration of an ezrin inhibitor, specifically the Rho kinase inhibitor Y27632, would be therapeutically effective in promoting endothelial cell proliferation and angiogenesis, or reducing severity of blood vessel damage.

However, as stated in the previous office actions, the results of these studies and derived from *in vitro* experiments or experiments in which HUVECs were administered to a mammal, rather than direct administration of any specific inhibitor. While these results may lead one of skill in the art to conclude that inhibition of ezrin would promote endothelial cell proliferation or angiogenesis, one of ordinary skill in the art would also know that previous studies have indicated that administration of the Rho kinase inhibitor Y27632 produced opposite results. As set forth in previous office actions, Uchida *et al* disclosed that administration of Y27632 inhibited angiogenesis (see Figs 1-3 of Uchida), while Xue *et al* demonstrated that administration of Y27632 inhibited hepatocellular metastases via anti-angiogenic mechanisms. Both Uchida and Xue present results derived from *in vivo* administration of an ezrin inhibitor, rather than *in vitro* administration or *ex vivo* administration of treated/transfected cells. Furthermore, administration of another Rho kinase inhibitor, fasudil, inhibited angiogenesis in an *in vivo* mouse corneal pocket assay (Hata *et al*, *Japanese J. Ophthalmology*, 2008, Vol. 52, p. 16-23, see especially p. 20 and Fig 5). While the Applicants' arguments regarding Shigata teaching prevention of neointimal lesion formation rather than angiogenesis are noted, the preponderance of evidence suggest that direct, *in vivo* administration of Rho kinase inhibitor such as Y27632 inhibits, rather than promotes, angiogenesis.

In regards to Applicants arguments that Van Nieuw Amerongen teaches Y27632-mediated inhibition of cell migration, rather than inhibition of proliferation, it is noted that Van Nieuw Amerongen teaches that migration is an important component of angiogenesis (p. 211, 1st column, 2nd paragraph). Thus, a person of skill in the art would suspect that inhibition of Rho-mediated signaling would inhibit angiogenesis by inhibiting cell migration.

Finally, regarding claims 66-68, drawn to methods of modulating endothelial cell proliferation comprising isolating endothelial cells from an individual, contacting the isolated endothelial cells *ex vivo* with am ezrin-modulating agent, a cytokine, angiogeneic factor, or hematopoietic factor, and then administering the isolated/treated endothelial cells to a mammal, it is noted that the specification teaches administration of endothelial cells which have been genetically modified by transfection with a dominant-negative ezrin. The specification does not provide guidance and examples of administering any ezrin-modulating agent to cells *ex vivo*, wherein this direct administration of the ezrin-modulating substance is sufficient to promote endothelial cell proliferation when the isolated/treated endothelial cells are subsequently administered to a subject. As set forth *supra*, one of ordinary skill in the art would predict that administering an ezrin-modulating agent such as Y27632 or fasudil to endothelial cells would result in decreased. It is also noted that the breadth of claims 66-68 is excessive in that they read on administration of any cytokine, any angiogenic factor, or any hematopoietic factor; however, the specification does not provide guidance or examples showing which of the many possible cytokines, angiogenic factors, or hematopoietic factors could be administered to endothelial cells in order to enhance prolifeation.

Therefore, contrary to the Applicants' arguments, one of ordinary skill in the art would reasonably conclude from the teachings of the prior art that administration of Y27632, regardless of whether the administration was localized administration of short-term administration, would inhibit endothelial cell proliferation and angiogenesis. Due to these contrary teachings in the art, a person of ordinary skill in the art would require further, undue experimentation in order to practice the claimed method.

Conclusion

No claim is allowable.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571)272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
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